

REMARKS

The Applicants have amended the Specification in order to cross-reference the related applications from which it claims priority.

The Examiner has withdrawn Claims 18-20 from consideration asserting that they are drawn to a non-elected invention. The Applicants have cancelled Claims 2, 8 and 18-20 without prejudice, amended Claims 1, 3 and 9-13, and added new Claims 21-40 to expedite the allowance of the remaining claims for business considerations. Support for the current amendments to the claims and for new Claims 21-40 can be found throughout the instant Specification, including in the original claims. Additional support for new Claims 21, 22, 27-29, and 34-36 can be found on Page 4, lines 3-12 of the Specification. Further support for new Claims 23-26, 30-33 and 37-40 can be found on line 26 of Page 2 through line 5 of Page 3, and on Page 4, lines 13-18 of the Specification. No new matter has been entered.

Currently amended Claims 1, 3, and 9-13, Original Claims 4-7, and 14-17, and New Claims 21-40 are pending. Reconsideration of the Application in view of the above amendments and the remarks below is respectfully solicited.

INFORMATION DISCLOSURE STATEMENT

The Examiner has indicated that references AW and BQ were not considered because they were not found in the parent file. The Examiner has also indicated that the listing of reference AW is incomplete.

The Applicants submit herewith a Supplemental Information Disclosure Statement, a Substitute Form-PTO 1449 containing the information requested by the Examiner, copies of the two above-identified references, *i.e.*, AW and BQ and a new submission, CM [Bukowski *et al.*, "Pegylated Interferon Alfa-2b Treatment for Patients with Solid Tumors: A Phase I/II Study," *J. Clin. Oncol.* **20**(18):3841-3849 (2002)]. The specific listings for references AW, BQ and CM in the Substitute Form-PTO 1449 are in bold for the Examiner's convenience. The Commissioner is hereby authorized to charge any required fees regarding the submission of this Supplemental Information Disclosure Statement to Deposit Account No. 19-0365.

The Applicants request that the Examiner consider references AW, BQ and CM, and make them of record.

THE PRESENT INVENTION IS DEFINITE

The Examiner has rejected Claim 8 under 35 U.S.C. § 112, second paragraph asserting that Claim 8 does not further limit the claim from which it depends and is therefore indefinite.

The Applicants have cancelled Claim 8 without prejudice. The pending claims are definite and fully comply with 35 U.S.C. § 112, second paragraph (as well as with 35 U.S.C. § 112, fourth paragraph).

In view of the above and foregoing withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully solicited.

THE PRESENT INVENTION IS NOT OBVIOUS

The Examiner has rejected Claims 1-9,12, and 14-17 under 35 U.S.C. § 103(a) as being unpatentable over Kirkwood *et al.*, [*J. Clinical Oncol.* **14**(1) 7-17 (1996)]; in view of Gilbert *et al.*, [US 5,951,974, filed 12/19/97, issued 9/14/99], Glue *et al.*, [US 5,908, 621, filed 4/29/97, issued 6/1/99] and further in view of Talpaz *et al.*, [Blood 92(10) 251a (1998)].

The Examiner asserts that Kirkwood *et al.* teach a method of treating treatment-naïve patients having resected cutaneous melanoma with interferon *alpha*-2b and that the treatment results in increased median relapse-free survival time and increased overall median survival time.

The Examiner asserts that Gilbert *et al.* teach that pegylated interferon *alpha*-2b increases circulating life, solubility, and decreases antigenicity. The Examiner further asserts that Glue *et al.* teach a method of using pegylated interferon *alpha* to treat viral infection that results in a decrease in side-effects normally associated with pegylated interferon *alpha*. The Examiner further asserts Talpaz *et al.* teach the use of pegylated interferon *alpha*-2b for the treatment of chronic myelogenous leukemia.

The Examiner asserts that it would have been obvious to substitute pegylated interferon *alpha*-2b for the unconjugated protein of Kirkwood *et al.* in view of the teachings of Gilbert *et al.*, Glue *et al.* and Talpaz *et al.* The Examiner also asserts that it would have been obvious to extend the treatment of Kirkwood *et al.* to treatment-experienced patients, patients intolerant to interferon *alpha*, and patients that are resistant to interferon *alpha*. The Examiner further asserts that it would have been obvious to one of ordinary skill in the art to optimize the dosages and treatment schedules recited in the claims.

The Applicants respectfully traverse the Examiner's rejection of Claims 1-9,12, and 14-17 under 35 U.S.C. § 103(a). The claimed invention is not obvious over Kirkwood *et al.*, in view of Gilbert *et al.*, Glue *et al.*, and/or Talpaz *et al.*

The present invention provides a method of treating a patient having melanoma that comprises administering a therapeutically effective dose of

pegylated interferon *alpha* for a time period sufficient to increase progression-free survival time. In addition, when the pegylated interferon-*alpha* administered is a pegylated interferon *alpha*-2b the therapeutically effective amount of pegylated interferon administered once a week is preferably about 3.0 micrograms/kg to about 9.0 micrograms/kg. Furthermore, the present invention provides methods that administer 6.0 micrograms/kg of pegylated interferon *alpha*-2b once a week for eight weeks, followed by one or more reductions in the weekly dosage to 3.0 or less micrograms/kg of pegylated interferon *alpha*-2b for the remainder of a five year treatment period.

Section 2143 of the MPEP states that in order to establish a *prima facie* case of obviousness, three requirements must be satisfied:

- (a) There must be some suggestion or motivation from the art cited to make the invention;
- (b) the combination of the cited art must teach and/or suggest all of the claim limitations; and
- (c) the cited art must provide a "reasonable expectation of success."

In the present case none of the requirements for *prima facie* obviousness have been met.

The Examiner freely admits that Kirkwood *et al.*:

- (i) fail to teach methods of treatment employing pegylated interferon *alpha*;
- (ii) fail to teach treatment of treatment-experienced patients;
- (iii) fail to teach the treatment of patients intolerant to interferon *alpha*; and
- (iv) fail to teach the treatment of patients that are resistant to interferon *alpha*.

Moreover, the Examiner admits that Kirkwood *et al.* fail to teach the dosages and treatment schedules of the present invention.

In an attempt to cure these deficiencies the Examiner applies Gilbert *et al.*, Glue *et al.*, and Talpaz *et al.* However, Gilbert *et al.* is drawn to

pharmaceutical compositions that comprise a specific positional isomer of a conjugated interferon and therefore, cannot make up for the insufficiencies of Kirkwood *et al.* Whereas Glue *et al.* demonstrate that pegylated interferon is better than the unconjugated interferon in the treatment of hepatitis C, Glue *et al.* also does not lead the skilled artisan to the present invention. Indeed, the broad dosage range of pegylated interferon *alpha*-2b taught as being safe and effective by Glue *et al.* does not encompass the higher dosages employed by the methods of the claimed invention. Furthermore, the Examiner has provided neither the requisite motivation to substantially alter the dosage regimen taught by Glue *et al.* to come to the present invention, nor the reasonable expectation of success that such alterations would be both safe and effective.

Talpaz *et al.* cannot overcome the shortcomings of Kirkwood *et al.*, in view of Gilbert *et al.*, and/or Glue *et al.* Indeed, Talpaz *et al.* provide preliminary results in a short Abstract that the authors themselves couch as merely suggesting that pegylated interferon “may provide improved tolerability ... and may demonstrate activity in patients with known interferon-alpha resistance” (emphasis added). Moreover, Talpaz *et al.* is drawn solely to the use of pegylated interferon *alpha*-2b in the treatment of chronic myelogenous leukemia, and is completely silent with regard to the treatment of melanoma.

Finally, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to optimize the dosages and treatment schedules to arrive at the present invention. However, without the requisite motivation and “reasonable expectation of success” provided by the prior art, it was by no means obvious at the time that the present invention was conceived how to formulate the safe and efficacious treatment of melanoma disclosed by the instant Specification.

Indeed, the CCPA has held in *In re Sebek* that:

“[W]e think that logic and reason compel the conclusion that in an area of technology shown to be **highly unpredictable** in process values, the **discovery of optimum values not in any way suggested by the prior art** is more likely to be **unobvious** than obvious within the meaning of §103.” [*In re Sebek* 175 USPQ 93, 95 (CCPA 1972) emphasis added].

The Applicants respectfully submit that at the time of the filing of the present application the treatment of melanoma was highly unpredictable. Furthermore, none of the references cited by the Examiner suggest that the unique dosage regimens of the present invention would likely be successful in the treatment of melanoma. Therefore, the present invention is not obvious over Kirkwood *et al.* in view of Gilbert *et al.*, Glue *et al.*, and Talpaz *et al.* Indeed, the skilled artisan is led to the present invention solely through the teachings of the instant Specification.

In view of the above and foregoing withdrawal of the rejection under 35 U.S.C. § 103(a) over Kirkwood *et al.*, in view of Gilbert *et al.*, Glue *et al.*, and Talpaz *et al.* is respectfully solicited.

The Examiner has also rejected Claims 1-8,10,11,13 and 14 under 35 U.S.C. § 103(a) as being unpatentable over Creagan *et al.*, [*J. Clinical Oncol.* 13(11) 1776-2783 (1995)]; in view of Gilbert *et al.*, [US 5,951,974, filed 12/19/97, issued 9/14/99], and further in view of Glue *et al.*, [US 5,908, 621, filed 4/29/97, issued 6/1/99].

The Examiner asserts that Creagan *et al.* teach a method of treating treatment-naïve patients and treatment-experienced patients with resected malignant melanoma using interferon *alpha*-2a, and teaches that it also benefits stage II patients. The Examiner asserts that Gilbert *et al.* teach that pegylation of interferon *alpha*-2b may be used to pegylate interferon *alpha*-2a. The Examiner further asserts that Gilbert *et al.* teach that pegylated interferon *alpha*-2b increases circulating life, solubility, and decreases antigenicity. The Examiner also asserts that Glue *et al.* teach a method of using pegylated interferon *alpha* to treat viral infection that results in a decrease in side-effects normally associated with pegylated interferon *alpha*.

The Examiner further asserts that it would have been obvious to substitute pegylated interferon *alpha*-2a for the unconjugated protein of Creagan *et al.* in view of the teachings of Gilbert *et al.* and Glue *et al.* The Examiner also asserts that it would have been obvious to extend such treatment to patients intolerant to interferon *alpha*, and to patients that are resistant to interferon *alpha*.

The Applicants respectfully traverse the Examiner's rejection of Claims 1-8,10,11,13 and 14 under 35 U.S.C. § 103(a). The claimed invention is not obvious over Creagan *et al.*, Gilbert *et al.*, and/or Glue *et al.*

The Examiner admits that Creagan *et al.* fail to teach methods of treatment with pegylated interferon, and fails to teach the treatment of patients intolerant to interferon *alpha* or resistant to interferon *alpha*. Moreover, the Examiner admits that Creagan *et al.* fail to teach the dosages and treatment schedules of the present invention. For the reasons provided above, neither Gilbert *et al.* nor Glue *et al.* can cure these deficiencies.

Moreover, the Federal Circuit has held that:

"[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed.Cir. 1991).

In the present case, neither Creagan *et al.*, Gilbert *et al.*, nor Glue *et al.*, alone or in any combination, teach or even suggest the specific dosage regimens taught and claimed by the present invention. More importantly, neither Creagan *et al.*, Gilbert *et al.*, nor Glue *et al.*, alone or in combination provides the requisite reasonable expectation of success for the treatment of melanoma by administering the specific dosage regimens of the present invention.

In view of the above and foregoing withdrawal of the rejection under 35 U.S.C. § 103(a) over Creagan *et al.*, Gilbert *et al.*, and Glue *et al.* is respectfully solicited.

No additional fees are believed to arise due to this filing, however, if any fees are required, the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 19-0365.

The Applicants believe that the next step in the prosecution of this Application should be in the form of a Notice of Allowance and such action is respectfully solicited.

If the Examiner should have any questions regarding this Amendment and/or patent Application, she is encouraged to contact the undersigned attorney.

Respectfully submitted,

A handwritten signature in black ink that reads "Michael D. Davis". The signature is written in a cursive, flowing style.

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